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An Easy and Versatile Approach for the Regioselective De-*O*-benzylation of Protected Sugars Based on the I_2/Et_3SiH Combined System

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Abstract: The use of cheap and easy to handle reagents, such as I_2 and Et_3SiH, at low temperature allows the regioselective removal of benzyl protecting groups from highly O-benzylated carbohydrates. The observed regioselectivity is dependent on the nature of the precursor, the least accessible carbinol often being liberated. A mechanistic investigation reveals that in situ generated HI is the promoter of the process, whereas the regioselectivity appears to be mainly controlled by steric effects. However, the presence of an electron withdrawing acyl protecting group can switch the regioselectivity to favour deprotection of the carbinol position farthest from the ester group. The protocol is experimentally simple and provides straightforward access in useful yields to a wide range of partially protected mono- and disaccharide building blocks that are valuable for the synthesis of either biologically useful oligosaccharides or highly functionalised chiral compounds. Partially protected sugars thus obtained can also be coupled in situ with a glycosyl donor, as illustrated by the one-pot synthesis of a Lewis X mimic from fully protected precursors.

Keywords: benzyl ethers · carbohydrates · protecting groups · regioselectivity

Introduction

The benzyl group is one of the most frequently used protecting groups in organic synthesis for carbinol derivatisation.[1] Several advantages justify the popularity of this protecting group: a) the protection step can occur under either acidic or basic conditions, b) a benzyl group can be installed at multiple positions of molecules rich in functional groups, such as carbohydrates, and c) the protecting group is stable under a wide range of chemical conditions and can be removed under mild conditions.[1] Hydrogenolysis is the most commonly used method for de-O-benzylation and is especially suitable for the total deprotection of poly-O-benzylated substrates. Consequently, benzyl protecting groups are frequently employed in organic synthesis for the manipulation of polyhydroxylated targets and their removal is often performed at advanced stages in synthetic schemes. Protected carbohydrates are frequently exploited as convenient precursors for chiral compounds[2] through synthetic schemes that routinely rely on O-benzylated intermediates. In addition, the use of O-benzylated saccharide derivatives allows tuning of the reactivity of carbohydrate building blocks in glycosylation chemistry; a large number of examples highlight the "arming" effect of benzyl groups on both glycosyl donors and acceptors in comparison with the depressed reactivity of sugars equipped with "disarming" acyl groups.[3] Furthermore, benzyl groups are widely used in stereocontrolled glycosylations in which protecting, but not participating, groups are needed on the glycosyl donor.[4]

Rapid access to partially protected building blocks is one of the most important goals[5] in modern organic synthesis. In this regard, several procedures for the regioselective de-O-benzylation of densely O-benzylated saccharide precursors have been described in the literature. Among these, only a few examples rely on controlled hydrogenolysis[6] and most approaches require acidic conditions. Indeed, the regioselective de-O-benzylation of saccharide compounds can be effected with stoichiometric amounts of strong, sensitive Lewis acids, such as $SnCl_4$ or $TiCl_4$,[7] excess alanes (diisobutylaluminium hydride (DIBAL), triisobutylaluminum (TIBAL)) at high temperatures[8,9] or under microwave activation,[10] BCl_3 at low temperature,[11] or excess $CrCl_2$ and LiI at high temperature.[12] In these cases, regioselectivity is critically dependent on the possibility of the saccharide substrate to generate a chelated structure with the Lewis acid present in each reagent system, whereas benzyl removal is accomplished by a nucleophilic agent introduced either as the counteranion of the chelated metal or as an independent species. Chelation control can also serve in the regioselective de-O-benzylation of non-saccharide substrates under acidic conditions.[13] Other regioselective de-O-benzylation approaches for carbohydrates require the pre-existence of suitable functionalities next to the site to be deprotected, such as a free hydroxyl[14] or allyl group.[15]

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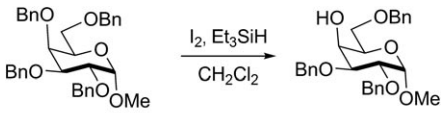
Very recently, Crich and Vinogradova showed that highly benzylated *manno*- and *rhamno*-derivatives can be deprotected with moderate selectivity at *O*-4 by treatment with a stoichiometric oxidant, such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[16] The primary positions can be de-O-benzylated (and concomitantly triethylsilylated) with excellent regioselectivity on prolonged exposure of benzylated mono-, di- and trisaccharides to the $Et_3SiH/[Co_2(CO)_8]$ combined system, at high temperature under a CO atmosphere.[17] Acetolysis is another approach that often leads to selective de-O-benzylation (and concomitant acetylation) of the primary positions, but in this case undesired cleavage of glycosidic bonds might occur.[18] Trimethylsilyl iodide (TMSI) has also been reported to produce selective de-O-benzylation of primary carbinols (via the corresponding trimethylsilyl ethers).[19]

Herein, we describe the wide and unprecedented scope of the I_2/Et_3SiH combined system in the regioselective de-O-benzylation of sugars. This reagent permits the smooth generation of anhydrous HI and several useful applications have already been established in our laboratory, for example, the combination of I_2 (stoichiometric) and Et_3SiH (catalytic) is an effective activating system for trihaloacetimidate glycosyl donors[20] and it was successively exploited by Takahashi and co-workers in their protocols aimed at the stereoselective synthesis of β-2,6-dideoxyglycosides.[21] An analogous stoichiometric combination of these reagents in methanol was found to be effective for the cleavage of benzylidene acetals.[22] Additionally, stoichiometric amounts of both I_2 and Et_3SiH allow glycosyl iodides to be generated from 1-*O*-acylated precursors within a few minutes; this rapid process has been incorporated into several procedures, which have lead to a variety of useful saccharide intermediates, such as 1,2-orthoesters,[23] ethylidenes,[23] glycals,[23] thio- and selenoglycosides,[24] and 2-*O*-deprotected allyl glycosides,[25] as well as glyco-conjugates with estradiol[26] or melanogenic 5,6-dioxyindole.[27] Additional synthetically useful applications of I_2/Et_3SiH have been reported by other groups for the regioselective reductive ring opening of benzylidenes,[28] the reductive Ferrier rearrangement of glycals[29] and the Friedel–Crafts cyclisation of aryl-substituted propargyl alcohols.[30]

The reaction of Et_3SiH and I_2 provides HI and Et_3SiI under very simple experimental conditions.[31] Given that HI and Me_3SiI are known reagents for ether cleavage,[19,32,33] we were prompted to explore the feasibility of applying the convenient I_2/Et_3SiH system to the deprotection of carbohydrates, with a special focus on the difficult issue of the regioselective de-O-benzylation of sugars.

Results and Discussion

In preliminary experiments, we examined the behaviour of tetra-O-benzylated methyl α-glycopyranosides in the presence of a slight excess of I_2 and Et_3SiH in CH_2Cl_2; the regioselective de-O-benzylation of these substrates immediately appeared to be a feasible task when working at low temperature. Galactoside **1** displayed a high propensity to be deprotected at *O*-4 (Scheme 1) and it was chosen as the model compound for optimising several experimental parameters, such as the order of reagent addition, their stoichiometry and the temperature (Table 1).



1 **2**

Scheme 1. Regioselective de-O-benzylation of model compound **1** (Bn = benzyl).

Table 1. The optimisation of the de-O-benzylation conditions.[a]

	Iodine [equiv]	Triethylsilane [equiv]	*T* [°C]	*t* [min]	Isolated yield of **2** [%]
1	0.5	0.5	−20	60	29
2	0.5	1.0	−20 to −5	60	35 (42)[c]
3	1.0	1.0	−20 to −15	50	43
4	1.25	1.25	−25 to 0	60	48
5	1.25[b]	1.25[b]	−20	30	45 (67)[c]
6	1.25	1.25	−20 to −10	15	60
7	1.25	1.25	−20	15	50

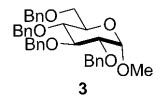
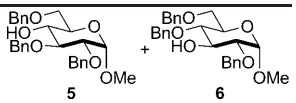
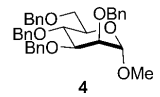
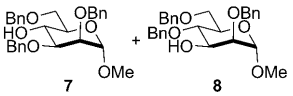
[a] General conditions: Et_3SiH was added at the indicated temperature to a solution of **1** and I_2 in anhydrous CH_2Cl_2. The reaction was quenched at the final temperature by addition of pyridine. [b] I_2 and Et_3SiH were premixed in CH_2Cl_2 and the resulting solution was added to **1** dissolved in CH_2Cl_2. [c] % conversion.

These experiments show the effectiveness of the simplest conceivable experimental procedure, the addition of Et_3SiH to a preformed solution of I_2 and the substrate in CH_2Cl_2. Other solvents, such as toluene, 1,2-dichloroethane, acetonitrile and dioxane, were found to be much less suitable and slower reactions were observed. Investigation into the stoichiometry of the reagents revealed that a slight excess of both is required to obtain high conversion of the starting material (compare Table 1, entries 4–7 with entries 1–3). Use of less than one equivalent of either reagent provided incomplete de-O-benzylation (Table 1, entries 1 and 2), suggesting that only HI, and not Et_3SiI, is responsible for the deprotection (see below for other evidence of this). Temperature was found to be critical for maximising the yield while allowing the reaction to proceed at an elevated rate. In fact, TLC analysis suggested that further deprotection of the mono-de-O-benzylated products was competitive with the initial de-O-benzylation step of the fully protected saccharide reagent. Thus, temperature control was pivotal for tuning the course of these potential processes. Under the optimised conditions (Table 1, entry 6), D-*galacto* precursor **1** provided 4-OH derivative **2** in an appreciable isolated yield (60%) after only 15 min at a temperature of between −20 and −10 °C. Upon further warming, the yield of **2** decreased owing to formation of larger amounts of products

that had undergone multiple de-O-benzylations. In comparison with other known procedures for the regioselective de-O-benzylation of sugars, this approach looked advantageous for several reasons, which include the reaction rapidity, the use of a slight excess of cheap and easy-to-handle reagents, and the non-demanding experimental precautions (no inert atmosphere was required for high yields to be achieved).

The procedure was then applied to *gluco*- and *manno*-precursors **3** and **4** (Table 2). A predominance of the 4-OH regioisomer was again recorded but in both cases the corresponding 3-OH regioisomer was isolated with the main product, as an inseparable mixture. The regioselectivity ratio was strongly dependent on the precursor and was much higher for *manno* precursor **4** (**7**/**8**, 8:1) than for *gluco* derivative **3** (**5**/**6**, 3.8:1). Interestingly, in these cases, de-O-benzylation started at lower temperatures than with the *galacto* precursor, but gradual warming of the reaction medium ensured completion in relatively short times.

Table 2. De-O-benzylation of tetra-*O*-benzylated *gluco*- and *manno*-pyranoside precursors.[a]

	Reagent	*t* [min]	*T* [°C]	Products, combined yield (conversion), regioisomeric ratio
1	 **3**	70	−55 to −30	 **5** + **6** 43 % (56 %), **5**:**6** 3.8
2	 **4**	75	−40 to −10	 **7** + **8** 44 % (60 %), **7**:**8** 8

[a] General conditions: Et_3SiH (1.25 equiv) was added to a solution of **3** or **4** and I_2 (1.25 equiv) in anhydrous CH_2Cl_2 at the starting temperature. The reaction was quenched at the final temperature by addition of pyridine.

Although the yields of these preliminary experiments might not appear especially high, it should be noted that standard routes to 4-OH compounds **2**, **5** and **7** from the corresponding methyl glycosides would require two additional synthetic steps (initial 4,6-*O*-benzylidenation followed by regioselective reductive ring opening) with chromatographic purifications. Additionally, it is pertinent that the recently reported attempt at regioselective deprotection of **4** with DDQ gave an inseparable mixture of **7** and **8** in a lower yield (31 %) and regioselectivity (**7**:**8**, less than 3:1),[16a] thus showing the potential of the approach presented herein with respect to the current state of the art of regioselective de-O-benzylation of carbohydrates.

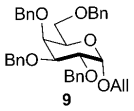
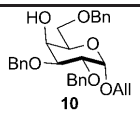
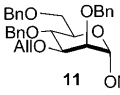
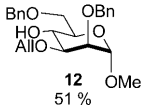
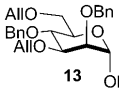
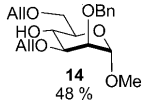
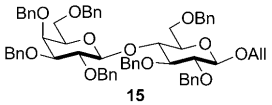
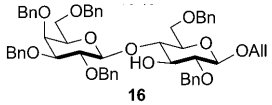
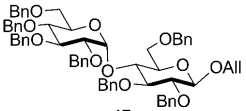
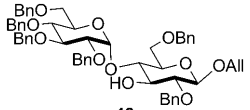
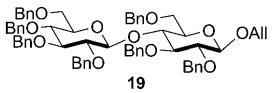
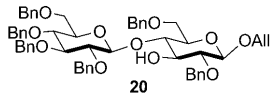
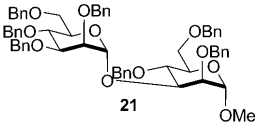
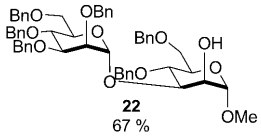
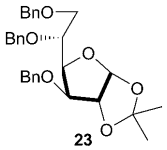
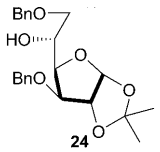
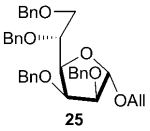
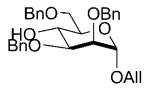
Other saccharide precursors bearing multiple benzyl protecting groups were then screened and further interesting results emerged (Table 3). Similar to α-methyl glycosides (Tables 1 and 2), α-allyl glycosides proved to be compatible with this protocol (compare Table 3, entry 1 with Table 1, entry 6), thus offering a useful extension to the reaction scope, especially in view of the wider chemical versatility of allyl aglycons. The stability of allyl groups installed on non-anomeric carbinols also led to an improvement in the regioselectivity of the de-O-benzylation of *manno*-configured sugars, for which partially O-allylated precursors can be effectively prepared by stannylidene-mediated protection.[34] As shown in Table 3, entries 2 and 3, 4-*O* deprotection of 3-*O*-allylated derivatives **11** and **13** occurred in satisfactory yields and high regioselectivity; unlike the behaviour of the corresponding 3-*O*-benzylated counterpart **4** (Table 2, entry 2), no products deprotected at O-3 were detected from these 3-*O*-allylated precursors.

The result obtained for allyl lactoside **15** was rather surprising (Table 3, entry 4), as it was quickly deprotected in very good yield at O-3 (*gluco* residue) rather than at the expected O-4′ position (*galacto* residue). This outcome broke the trend inferred from Tables 1 and 2 (4-OH products in all cases); the previously observed higher reactivity of glucose compared with galactose (compare activation temperatures in Tables 1 and 2) was initially considered in order to account for the apparently anomalous result. However, this hypothesis was immediately contradicted by results obtained from other disaccharide precursors **17**, **19** and **21** (Table 3, entries 5–7); regardless of the nature of the saccharide components, these compounds were selectively deprotected at the secondary carbinol of the reducing terminus adjacent to the glicoside bond. Very interestingly, 3-*O*-linked *manno*-disaccharide **21** (Table 3, entry 7) was preferentially deprotected at the axial *O*-2 position, oriented *cis* to the encumbered 3-*O*-glycosylated position, rather than at *O*-4. Notably, the deprotection yields of disaccharides were typically higher than for the monosaccharide precursors despite the larger number of potential deprotection events. Also worthy of note is the stability of the glycoside linkages on the disaccharides under the acidic conditions employed, despite the "arming" effect of the benzyl protecting groups, which is expected to facilitate acid-promoted scission of inter-saccharide linkages.[35]

As with monosaccharide and disaccharide precursors, furanoside derivatives displayed a peculiar regioselectivity trend. Glucofuranoside **23** (Table 3, entry 8) was selectively de-O-benzylated to give 5-OH regioisomer **24** in a comparable yield (58 %) to that obtained with $TiCl_4$.[7b] This was the only case found in which the Et_3SiH/I_2 system gave both a yield and regioselectivity similar to previously established procedures. Mannofuranoside **25** (Table 3, entry 9) was also debenzylated at *O*-5, but in this case the putative furanoside intermediate deprotected at *O*-5 evolved to give pyranoside **26**,[36] which has a free OH at *C*-4, and minor amounts of an unidentified product (ca. 10 %) with neither a free hydroxyl group nor the allyl aglycon.[37]

At this stage, a general survey of the obtained results and their comparison with previously reported approaches indicated an unprecedented direction of regioselectivity. As mentioned above, only the *O*-4 deprotection of monosaccharides resembles the results described by Crich (stoichiometric DDQ), the applicability of which, however, is re-

Table 3. Regioselective de-O-benzylation of pyranoside or furanoside monosaccharides, and disaccharides.[a]

	Reagent	T [°C]	t	Product, isolated yield (conversion)
1	 **9**	−40 to −25	50 min	 **10** 67 %
2	 **11**	−60 to 0	2.5 h	 **12** 51 %
3	 **13**	−65 to −5	2.5 h	 **14** 48 %
4	 **15**	−15	25 min	 **16** 83 %, (97 %)
5	 **17**	−60 to −20	1 h	 **18** 73 % (93 %)
6	 **19**	−60 to −20	1.5 h	 **20** 96 %
7	 **21**	−65 to +10	2.5 h	 **22** 67 %
8	 **23**	−60 to −20	1 h	 **24** 58 %
9	 **25**	−60 to −20	75 min	 **26** 55 %

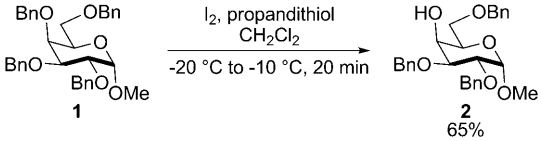
[a] General conditions: Et_3SiH (1.25 equiv) was added to a solution of the benzylated sugar and I_2 (1.25 equiv) in anhydrous CH_2Cl_2 at the starting temperature. The reactions were quenched by addition of pyridine (entries 1–3) or solid $NaHCO_3$ (entries 4–9; 2.5–5 equiv) at the final temperature.

stricted to *manno*- and *rhamno*-configured substrates to date.[16a]

To better explain the origin of the regioselectivity obtained, investigations were carried out to ascertain whether HI was actually the agent responsible for the deprotection. To this end, *galacto* precursor **1** was treated with a mixture of I_2 and propandithiol, in accordance with the procedure described some years ago by Koreeda and co-workers for the in situ generation of anhydrous HI.[38] As expected, the reaction once more afforded free 4-OH galacto derivative **2** in high yield upon exposure to I_2 (0.6 equiv) and propandithiol (1.2 equiv; Scheme 2). Under these conditions, the reaction rate and yield were both similar to those observed with I_2 and Et_3SiH. This outcome supports the hypothesis that in situ generated HI acts as the de-O-benzylation agent.[32] On the other hand, the negligible contribution of Et_3SiI to the process is supported by the reported stability at 0 °C of saccharide benzyl ethers upon exposure to Me_3SiI, which is supposedly more reactive in ether cleavage reactions than Et_3SiI, under the conditions adopted for the synthesis of glycosyl iodides of per-O-benzylated sugars.[39] Additionally, in sharp contrast with the results found for the I_2/Et_3SiH system, the regioselectivity of Me_3SiI-mediated de-O-benzylation leads to preferential modification of the sterically more accessible primary positions.[19] In fact, only in the reaction described in Table 3, entry 3 did we isolate minor quantities (5 %) of the 4-*O*-triethylsilylated ether of **14**.

On the basis of this evidence and according to a well-established general mechanism for ether scission,[32b] HI is expected to activate the benzyloxy group by O-protonation to favour the subsequent benzyl removal by nucleophilic attack of the iodide anion and release of the alcohol. Consistently, benzyl iodide was isolated as a by-product of the reactions.

Once we had identified the actual promoter of the process, some consideration was given to rationalising the origin of the observed regioselectivity. Unlike many of the previously reported methods operating under Lewis acidic conditions, HI-induced de-O-benzylation cannot be regioselectively controlled by chelation effects. On the other hand, we observe that in all examined cases the liberation of poorly accessible carbinols was favoured and in no case were O-benzylated primary positions significantly affected. Thus, a reasonable mechanistic sketch could involve the initial HI-promoted O-protonation occurring reversibly at the benzyloxy groups; the following de-O-benzylation step, promoted by the nearby iodide anion, is somehow kinetically controlled by the relief of the steric strain associated with the expulsion of the benzyl group. This effect could account for both the preferential deprotection (Tables 1 and 2) at the *O*-4 position,



1 → **2** 65%

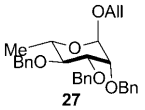
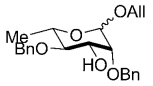
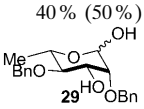
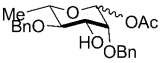
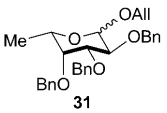
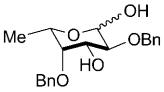
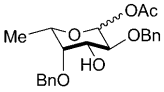
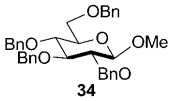
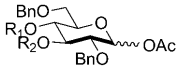
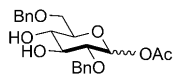
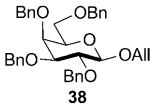
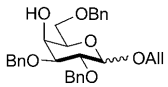
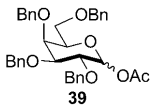
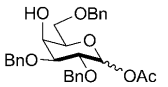
Scheme 2. Regioselective de-O-benzylation of model compound **1** with I_2 (0.6 equiv) and propandithiol (1.2 equiv).

the most encumbered for pyranoside monosaccharides, and the highest regioselectivity associated with removal of the axially oriented galactose 4-*O*-benzyl group (compare Tables 1 and 2). Furthermore, the apparently anomalous behaviour of disaccharide derivatives (Table 3, entries 4–7) is consistent with this hypothesis if the steric crowding around a benzylated carbinol group flanking a glycosidation site is acknowledged. Similar reasoning can also be applied to rationalise the liberation of the 5-OH in furan derivatives (Table 3, entries 8 and 9), which, in the case of entry 8, fortuitously provides a result similar to a de-O-benzylation occurring under chelation control. Some cases of acid-promoted ether or acetal scission that appear in the literature seem to be governed by the "steric-strain release effect" invoked here.[40]

To further extend the substrate scope of this reaction, other kinds of precursor, such as 2,3,4-tri-*O*-benzylated 6-deoxy pyranosides and β-configured 2,3,4,6-tetra-*O*-benzylated glycopyranosides, were exposed to the I_2/Et_3SiH system. Initial experiments were frustrating as complex mixtures were observed by TLC analysis. However, upon pyridine or lutidine quenching, the TLC profile of the reaction mixtures became simpler and most products displayed higher mobility than during the course of the reaction. This apparently strange observation was ascribed to the in situ generation of glycosyl iodide intermediates as a consequence of the higher anomeric reactivity of 6-deoxyglycosides and β-*O*-linked glycosides, which could result in a fast HI-promoted expulsion of the aglycon alcohol. Glycosyl iodides of "armed" densely O-benzylated sugars are not very stable, so that they are probably degraded under TLC elution conditions to give more polar hydrolysis products. Experiments conducted with varied amounts of I_2 and Et_3SiH showed that anomeric iodination was faster than de-O-benzylation at any site, and thus part of the I_2/Et_3SiH reagent was consumed for this process. Interestingly, quenching of the reaction with bases as mild as pyridine or lutidine induced reattachment of the initial aglycon alcohol with poor selectivity to give mixtures of α- and β-glycosides starting from anomerically pure substrates. These observations led us to foresee that addition of sufficient I_2 and Et_3SiH could induce concomitant de-O-benzylation together with the faster anomeric iodination. Thus, upon quenching, the reaction would yield partially protected derivatives as anomeric mixtures. This overall result could be very useful if the synthetic elaboration of the sugar entails subsequent removal of the aglycon, as in, for example, the preparation of glycosyl donors for oligosaccharide synthesis.

After several experiments the use of 1.8 equivalents of both I_2 and Et_3SiH emerged as the best option for performing the regioselective de-O-benzylation of sugars that are especially reactive at the anomeric positions. Application of these conditions to L-*rhamno* precursor **27** (Table 4, entries 1–4) resulted in regioselective deprotection at *O*-3, whereas *O*-4 deprotection had previously been recorded in the presence of the bulkier benzyloxy group at *C*-6 (Table 2, entry 2) or under the DDQ methodology.[16a] Different

Table 4. Regioselective de-O-benzylation of 6-deoxy glycopyranosides and monosaccharide β-pyranosides.[a]

	Reagent	*T* [°C]	*t*	Quenching conditions	Products, yield (conversion)
1	 **27**	−60 to 0	2 h	A	 **28** (α/β 10) 42 % (52 %)
2	**27**	−60 to 0	2 h	B	**28** (α/β 1) 40 % (50 %)
3	**27**	−60 to 0	2 h	C	 **29** 38 % (43 %) + **28** 17 % (20 %)
4	**27**	−60 to 0	1 h	D	 **30** (β/α 10) 57%
5	 **31**	−65 to 0	2 h	C	 **32** (α/β 1.5) 61 %
6[b]	**31**	−65 to 0	2 h	D	 **33** (α/β 1) 67 %
7[b]	 **34**	−25 to −5	1 h	D	 **35** R_1: H, R_2: OBn **36** R_1: OBn, R_2: H 31 % (**35**/**36** ≈2)  **37** 19 %
8	 **38**	−60 to −10	80 min	A	 **10** (α/β 1) 50 % (62 %)
9	 **39**	−30 to −15	40 min	D	 **40** 46 %

[a] General conditions: Et_3SiH (1.8 equiv) was added at the starting temperature to a solution of the benzylated sugar and I_2 (1.8–2.1 equiv) in anhydrous CH_2Cl_2. The mixture was allowed to warm up to the final temperature. The reaction was quenched at the final temperature according to the following conditions A–D, and then the reaction vessel was allowed to warm to RT. Conditions A: allyl alcohol (5 equiv) and $NaHCO_3$ (5 equiv); B: allyl alcohol (5 equiv) and lutidine (5 equiv); C: saturated aqueous sodium carbonate; D: a solution of lutidine (7 equiv) and acetic acid (4 equiv) in CH_2Cl_2. [b] Products **33** and **37** were slightly contaminated by an unidentified regioisomer.

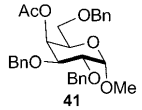
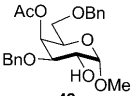
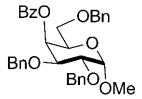
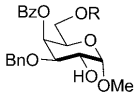
quenching conditions (Table 4, conditions A–D) were also developed in order to tune the anomeric composition of the product, or even to change the nature of the anomeric sub-

stituent. These data show that reattachment of the aglycon alcohol can proceed with variable stereoselectivity according to the nature of the base (Table 4, entries 1 and 2). On the other hand, hydrolysis of the glycosyl iodide was also carried out by quenching with saturated aqueous sodium bicarbonate (Table 4, entry 3) even though partial reattachment of the original alcohol aglycon was also recorded. Even more interestingly, the aglycon of the starting compound could be exchanged for a synthetically versatile acetate group upon quenching with a premixed solution of acetic acid and lutidine in CH_2Cl_2 (Table 4, entry 4). The quenching with pyridine, applied in our initial experiments on precursors unaffected at the anomeric position by I_2/Et_3SiH (Tables 1–3), was soon abandoned after consistently isolating glycosyl pyridinium species that reduced the overall yield of the process.

Application of these procedures to L-fucose confirmed the greater amenability of 6-deoxy sugars to *O*-3 deprotection with concurrent modification at the anomeric position (Table 4, entries 5–6). Interestingly, per-O-benzylated β-glucoside **34** and β-galactoside **38** also revealed anomeric reactivity towards I_2 and Et_3SiH, as shown by the aglycon exchange in Table 4, entry 7 and the partial anomerisation in Table 4, entry 8. The regioselectivity of the de-O-benzylation was consistent with that of the corresponding α-pyranoside precursors (compare with Tables 1 and 2), and small amounts of 3,4-diol **37** (slightly contaminated by another 1-*O*-acetylated derivative) were also isolated from the *gluco* precursor. The 1-*O*-acetylated *galacto* derivative **39** (Table 4, entry 9), which is prone to anomeric iodination with I_2/Et_3SiH,[23] also reacted with a regioselectivity mirroring the behaviour of the corresponding α-methyl glycoside **1** (Table 1). At this stage it is interesting to recall that no evidence of HI-promoted de-O-allylation was recorded for β-*O*-allylated disaccharides **15**, **17**, and **19** (Table 3, entries 4–6). This evidence highlights that de-O-benzylation of disaccharide substrates is much faster than their anomeric iodination, in stark contrast with the behaviour of monosaccharide β-glycosides.

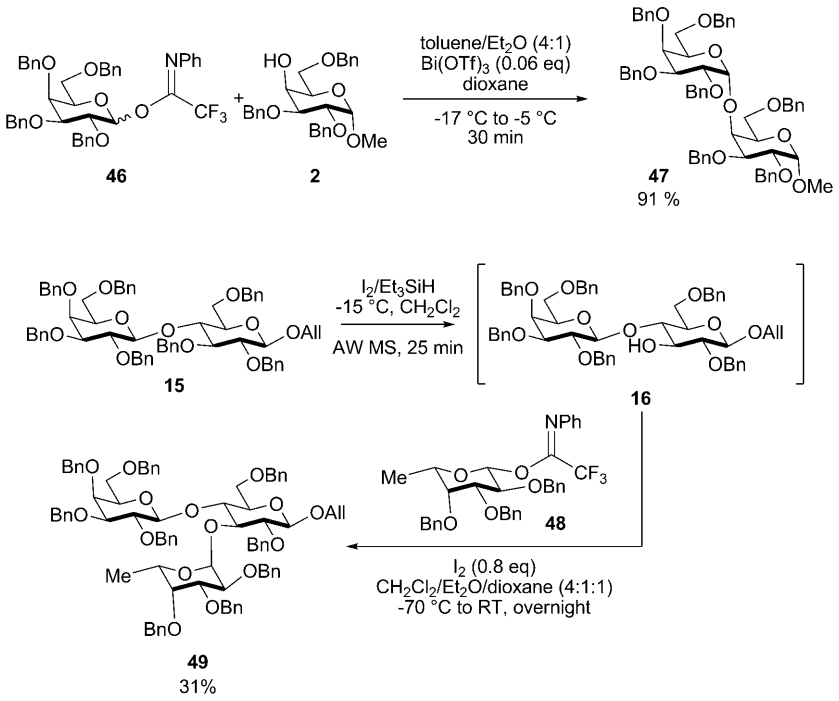
A further extension of the reaction scope was pursued by examining the effect of acyl protecting groups on substrates containing multiple benzyl groups. The electron withdrawing properties of acyl groups were expected to reduce the basic character of adjacent benzylated oxygen atoms, interfering with the preliminary protonation of the benzyloxy group necessary to trigger the iodide-induced benzyl removal. This effect could switch the normal regioselectivity (controlled by steric factors) to favour deprotection of carbinol sites further from the acyloxy groups. To test this effect, compound **2** was acetylated and benzoylated under standard conditions to yield derivatives **41** and **43** (Table 5). Both derivatives were then exposed to the I_2/Et_3SiH system at low temperature. Interestingly, the regioselectivity of the process was significantly influenced by the presence of the ester functionality, the benzyl group further away (at *O*-2) was preferentially removed in synthetically useful yields (Table 5, entries 1 and 2). In these cases minor amounts of pure by-products were isolated. In particular, compound **41** (Table 5, entry 1) also gave the 6-*O*-debenzylation product in 12% yield, as well as minor amounts (less than 10%) of the 3-*O*-deprotected derivative. This was the only case in which liberation of the primary carbinol was observed to an appreciable extent. Starting from compound **43** (Table 5, entry 2), the liberation of the 2-OH was partially accompanied by 6-*O*-triethylsilylation (17%). As mentioned above, triethylsilylation of benzylated substrates is an uncommon event upon treatment with I_2/Et_3SiH. The directing effect of acyl groups on regioselectivity further expands the synthetic potential of this method; selective 2-*O*-deprotection, which has never been observed when starting from per-O-benzylated monosaccharides (Tables 1, 2 and 3), are now possible starting from 4-*O*-acylated precursors.

Table 5. Regioselective de-O-benzylation of 4-*O*-acylated galactopyranosides.[a]

	Reagent	*t* [min]	*T* [°C]	Product, yield [%]
1	 **41**	90	−20 to −5	 **42** 43 %
2	 **43**	45	−20 to −5	 **44** R: Bn 46 % **45** R: TES 17 %

[a] General conditions: Et_3SiH (1.25 equiv) was added to a solution of **41** or **43** and I_2 (1.25 equiv) in anhydrous CH_2Cl_2 at the starting temperature. The reaction was quenched at the final temperature by addition of pyridine. Bz = benzoyl, TES = triethylsilyl.

The usefulness of this methodology as a tool to streamline the synthesis of biologically useful oligosaccharides was demonstrated by use of acceptors **2** and **16**, rapidly prepared in high yields as shown above. Coupling of acceptor **2** with galactosyl trifluoroacetimidate[41] donor **46** under catalytic activation by $Bi(OTf)_3$[42] quickly afforded protected galabiose **47** (Scheme 3) in a very high yield and with α selectivity. Galabiose is contained in a range of biologically relevant oligosaccharide sequences, and this disaccharide fragment is frequently investigated for its potential role in tuning the adhesion of pathogenic bacteria.[43] In another application, the de-O-benzylation procedure was incorporated into a one-pot sequence yielding Lewis X mimic **49**, in which the glucosamine residue is replaced by glucose (Scheme 3).[44] For this purpose, fully protected lactose **15** was deprotected at *O*-3 as shown in Table 3, entry 4, then fucosyl imidate **48**[45] was added directly to the reaction vessel with additional iodine.[20,46,47] The procedure afforded **49** in an acceptable 31% overall yield and, to the best of our knowledge, this is the first example in which a benzyl ether cleavage has been applied to a one-pot sequence for oligosaccharide synthesis. Indeed, reductive opening of benzylidenes is the most frequently pursued strategy for liberating a carbinol position in one-pot protocols of carbohydrate derivatisation and oligosaccharide synthesis.[5,48]



Scheme 3. Application of regioselectively deprotected products in the synthesis of biologically relevant oligosaccharides (All = allyl; AW MS = acid washed molecular sieves).

Conclusion

In this paper, we have demonstrated that the I_2/Et_3SiH combined system is a very useful reagent for the regioselective de-O-benzylation of highly O-benzylated substrates. The HI generated in situ appears to be the actual promoter of the process. Synthetically useful yields are frequently achieved to give partially protected building blocks that are otherwise accessible only through longer synthetic sequences. The obtained results show that sterically hindered benzyl groups are preferentially removed and the relief of steric strain appears to be the main factor influencing the regioselectivity. This effect could explain other known selective processes of ether and acetal scission that occur under acidic conditions and might be exploited in the design of new, selective, acid-promoted processes. Consistent with this mechanistic view, each group of substrates examined displayed a well defined regioselectivity trend; tetra-O-benzylated hexopyranoside monosaccharides are preferentially deprotected at *O*-4, hexofuranosides at *O*-5, 6-deoxy pyranosides at *O*-3, per-O-benzylated disaccharides at a secondary carbinol site of the reducing terminus adjacent to the glycoside bond. Interestingly, the regioselectivity of the process can also be switched by the insertion of acyl protecting groups on the substrate that result in de-O-benzylation at the site farthest from the acylated position.

Application of the reagent system (with an appropriate stoichiometry) to substrates that are especially reactive at the anomeric position (6-deoxy glycopyranosides and monosaccharide β-pyranosides) causes rapid anomeric iodination at low temperature alongside the de-O-benzylation. However, the intermediate glycosyl iodides generated are reactive enough to be converted into a variety of synthetically useful products upon suitable quenching.

As demonstrated by the synthesis of Lewis X mimic **49**, the de-O-benzylation protocol can also be incorporated into one-pot procedures for oligosaccharide synthesis with an unprecedented use of the benzyl group as a transient protecting group.

In addition to its wide applicability, the disclosed protocol exhibits a broad range of practical advantages over many of the current methodologies for regioselective de-O-benzylation; reactions proceed rapidly at low temperatures and are performed without adopting inert atmospheres and the reagents are cheap and easy to handle and can be used in slight stoichiometric excesses.

Experimental Section

General procedure for de-O-benzylation with I_2 and Et_3SiH: Anhydrous CH_2Cl_2 (16–20 mL mmol^{-1} I_2) was added to the poly-O-benzylated derivative and I_2 at room temperature (see Tables for the relative amounts of reagents). After complete dissolution, the mixture was cooled to the starting temperature of the reaction (see Tables) and then Et_3SiH (see Tables for the relative amount) was added by syringe. The reaction mixture was allowed to gradually warm or maintained at the same temperature (see Tables) until TLC analysis displayed the optimal extent of conversion. The reaction was quenched as indicated in the Tables. For conditions A (Table 4), allyl alcohol (5 equiv) and solid $NaHCO_3$ (5 equiv) were added sequentially. For conditions B, allyl alcohol (5 equiv) and lutidine (5 equiv) were added sequentially. For conditions C, saturated aqueous sodium carbonate (5 mL mmol^{-1} I_2) was added. For conditions D, a solution of lutidine (7 equiv) and acetic acid (4 equiv) in CH_2Cl_2 (3 mL mmol^{-1} I_2) was added. The mixture was allowed to warm to RT and then diluted with CH_2Cl_2. The organic phase was washed with water containing sodium thiosulfate (to remove residual amounts of iodine). The aqueous phase was re-extracted with CH_2Cl_2, and the collected organic phases were dried and concentrated in vacuo. Silica-gel flash column chromatography (eluent: hexane/ethyl acetate mixtures) yielded the de-O-benzylated products reported in the tables.

Acknowledgements

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